Searching for a unicorn:

Navigating stakeholder perspectives when selecting outcomes for outpatient trials

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Disclosures

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- Endpoint Health
- Entegrion LLC
- bioMerieux
- Abbott
- Astra Zeneca

Patents for risk stratification in septic shock held by CCHMC

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- The ACTIV program and the ACTIV-6 team
- ACTS BERD
- NCATS
- PCORnet
- NHLBI's CONNECTS Science Core
- Vanderbilt Institute for Clinical and Translational Research
- VB INSIGHTS

The Economist

What is an outcome?

Different kinds of outcomes

How outcomes are used for decision-making

Consequences for choosing the wrong outcome

Factors to consider when selecting outcomes

Selecting outcomes for outpatient trials in a pandemic

What is an outcome?

In the context of a clinical trial, it is the main piece of information that is used to make decisions about the success or failure of the intervention

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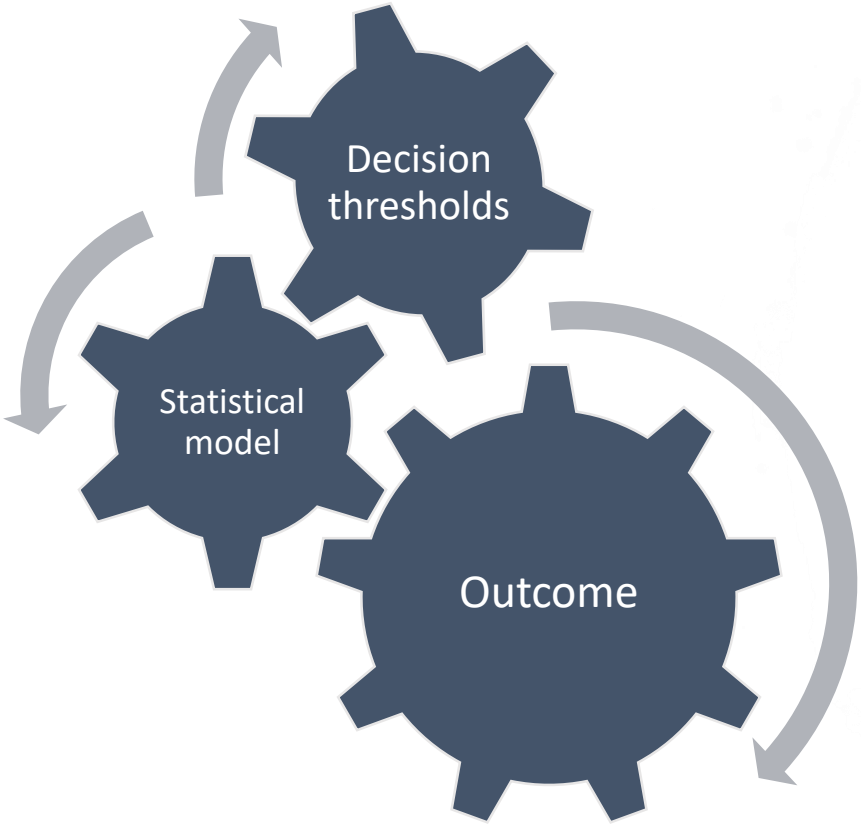
The purpose of this study is to see if the medicine **keeps you alive**



➔ Does the intervention work?

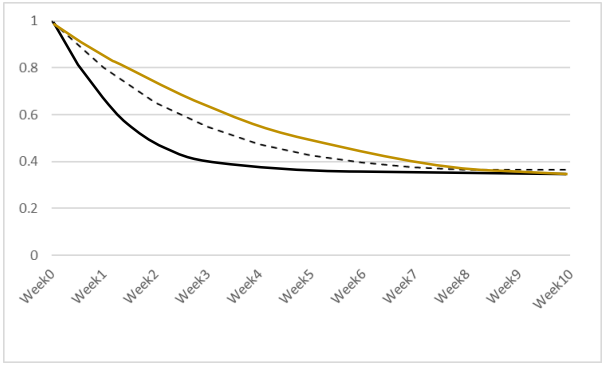
For each situation, we need to decide how to ‘measure’ the information

The purpose of this study is to see if the medicine keeps you alive

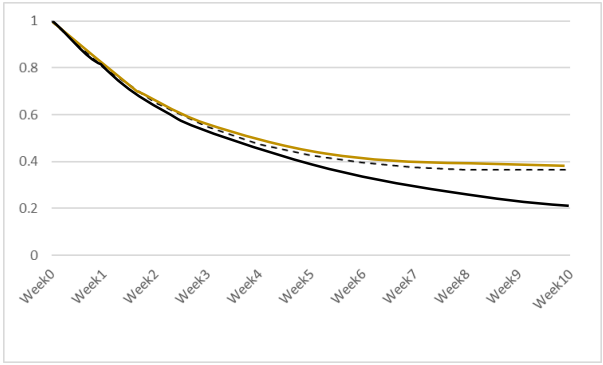
- Does it matter when the death occurred?
- Does the manner of death matter?
- How long do you watch people?
- Is death measured as a *yes* or *no* variable?
- How do you accurately measure death?

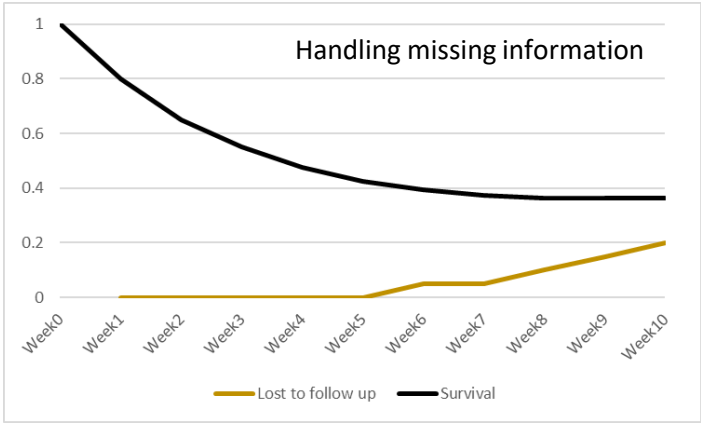
The purpose of this study is to see if the medicine keeps you alive

Time to death might be different, but total mortality may not be



Not observing long enough might miss differences





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Should we prioritize symptoms or signs ?

Patient Reported Outcomes –v– Researcher Observed Outcomes

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Symptoms or signs ?

Patient Reported Outcomes –v– Researcher Observed Outcomes

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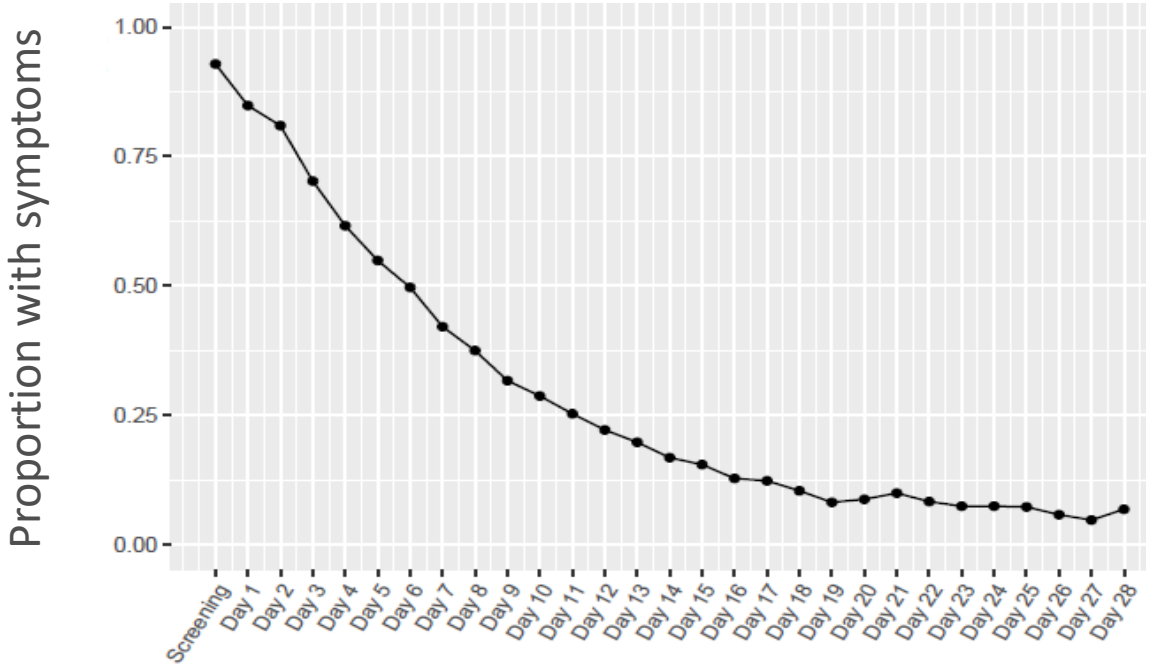

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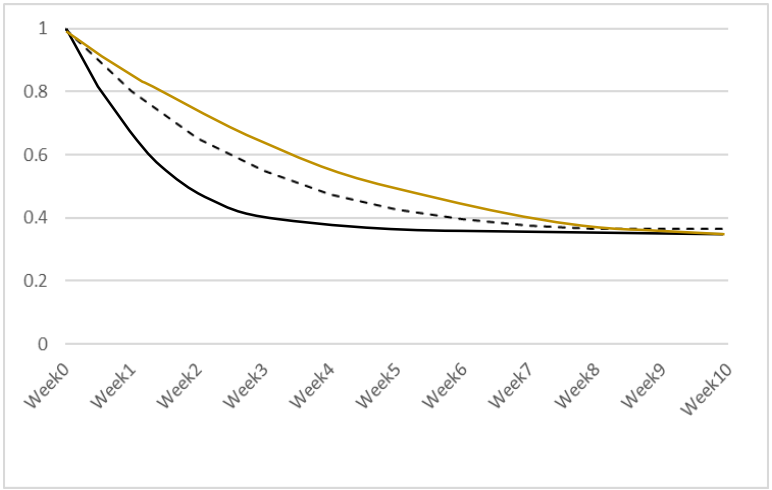
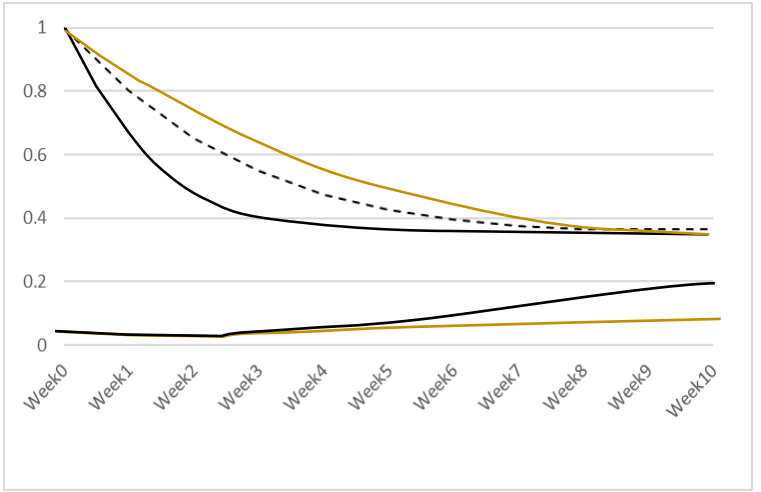
Time to recovery might be different, but no difference on longer term outcomes



What about opposite effects on symptoms and mortality?



Composite outcomes may help somewhat

- Composite outcome of rehospitalization or death at a singular time point
- Days alive and out of hospital
- Progression to next highest level of care
- Global ranks, win ratios and similar

Safety measurements are usually made on a separate scale so a qualitative risk/benefit trade-off needs to be made

Could we do better?

Key attributes of a good outcome measure

- It gives credit to a treatment for good outcomes that matter to patients
- It penalizes a treatment when the treatment causes serious adverse outcomes
- It has as few tied values as possible; the more continuous the measure the higher the statistical power and the lower the sample size
- It is measured over the relevant clinical time course
- It does not have its interpretation clouded by rescue therapy or intervening events

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Now presenting……

A full spectrum scale for evaluating treatments in Covid-19

Samn-Perelli Fatigue Scale

MRC Dyspnoea Scale

Symptom burden

Modified mRS

Outpatient organ support

Adapted SOFA

CTCAEs

Domain	None (0)	Mild (1)	Moderate (2)	Severe (3)	Life threatening (4)	Score
If the patient was not admitted on this day, complete the following:						
Fatigue[1]	As fully alert and wide awake as I was before becoming sick	A little tired, let down	Moderately to extremely tired, very difficult to concentrate	Completely exhausted, unable to function effectively	N/A	____
Dyspnea[2]	None OR I only get breathless with strenuous exercise, when hurrying on level ground or walking up a slight hill	Since becoming sick, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on level ground.	Since becoming sick, I stop for breath after walking about 100 yards or after a few minutes on level ground.	Since becoming sick, I am too breathless to leave the house or I am breathless when dressing.	N/A	____
Symptoms[3]	No symptoms due to my COVID-19 diagnosis	I have experienced more than 1 but less than 5 symptoms of COVID-19.	I am experiencing between 5 to 9 symptoms of COVID-19.	I have 10 or more symptoms of COVID-19.	N/A	____
Functional status[4]	After being diagnosed with COVID-19, I am still able to do all tasks without help.	After my COVID-19 diagnosis, I can complete most tasks without help but unable to carry out all previous activities.	After my COVID-19 diagnosis, I now require help with most tasks, but can walk without assistance.	After my COVID-19 diagnosis, I need help with all tasks and am unable to complete self-care.	N/A	____
If the patient was at home but required organ support, defined as RRT developed during COVID admission or supplemental oxygen that is new since hospitalization to maintain oxygen saturation above 90%, on this day, score is 4[9]						
If the patient was an inpatient at any time on this day, complete the following:						
Respiration[5] PaO2/FiO2, mm Hg (kPa) SpO2 & oxygen delivery (without/with ventilation)	≥ 400 (53.3) SpO2 ≥ 97% on room air -OR- SpO2 97% to 100%	300-399 (40-53.2) SpO2 92% to 96% on room air -OR- n/a	200-299 (26.7-39.9) or <200 (26.7) without respiratory support Supplemental O2 to maintain SpO2 ≥ 92% -OR- SpO2 92% to 96% on FiO2=0.3	100-199 (13.3-26.5) with respiratory support N/A -OR- FiO2 0.31 to 0.69 to maintain SpO2 ≥ 92%	<100 (13.3) with respiratory support N/A -OR- FiO2 ≥ 0.7 to maintain SpO2 ≥ 92%	____
Coagulation[6] Platelets, x10³/µL	≥ 150	100-149	50-99	20-49	<20	____
Liver[7] Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)	____
Cardiovascular[8]	MAP ≥ 70 mm Hg	MAP <70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)	Dopamine > 5 OR epinephrine ≤ 0.1 OR norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1, norepinephrine > 0.1	____
Central nervous system[9] Glasgow Coma Scale	15	13-14	10-12	6-9	<6	____
Renal[10] Creatinine, mg/dL (µmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-400)	>5.0 (400)	____
For all patients, complete the following:						
SAE[11] One SAE per row	Based on specific SAE	Based on specific SAE	Based on specific SAE	Based on specific SAE	Based on specific SAE	____
Death	N/A	N/A	N/A	N/A	N/A	150

Outpatient

Inpatient

SAEs and death

A full spectrum scale for evaluating treatments in Covid-19

Samn-Perelli Fatigue Scale

MRC Dyspnoea Scale

Symptom burden

Modified mRS

Outpatient organ support

Adapted SOFA

CTCAEs

Outpatient

Inpatient

SAEs and death

Key attributes of a good outcome measure (Contd.)

- It can be meaningfully translated into information that matters to policy makers, guideline writers, regulators, insurers, researchers, providers, and patients
- It is properly contextualized to the impact on individual and public health

We are still not yet ready to try and find the unicorn

Both failing an intervention or passing an intervention have risk and reward, the consequences of which peak around the time of seeking approval for use

Some Consequences of Decision Making

- Failing an intervention inappropriately prevents therapies with a favorable risk-benefit profile from benefitting people
- Accidently promoting a therapy that has an unknown or unfavorable risk/benefit profile into common practice carries financial, reputational and other risks and rewards
- Accidently promoting a therapy that has an unknown or unfavorable risk/benefit profile into common practice could adversely affect the health of people

Motivating factors

Is it generally in the interest of the researcher to use outcomes that prioritize **sensitivity over specificity ?**

E.g. fail fast if there is no signal and reduce the evidence needed to draw conclusions and promote the next step towards practice with the possibility that ineffective or harmful intervention would move forward

Is it generally in the interest of science and public health to use outcomes that prioritize **specificity over sensitivity ?**

E.g. prevent unsafe or ineffective interventions moving into practice at the expense of some therapies that might have a favorable risk benefit profile

Motivating factors

Is it generally in the interests of the researcher, provider, and participant to emphasize **pragmatism over control ?**

E.g. cost, bias minimization, ease of integrating research into care, minimal data collection burden, acceptability of results by providers

Is it generally in the interests of science to use outcomes that prioritize **control over pragmatism ?**

E.g. ensure that science is informed by accurate knowledge and people

?

Common wisdom can be upended by circumstances

Go fast, minimize contact

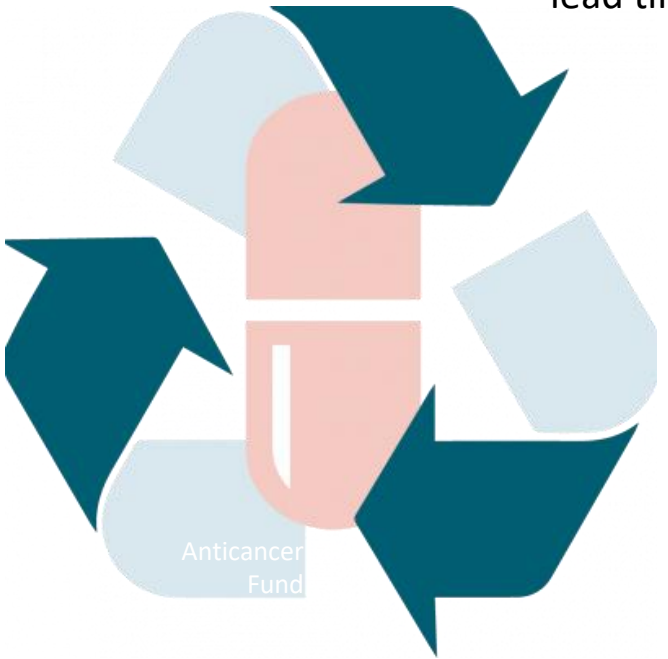
Save lives

Prevent progression

Feel better faster

Known risk profile

Familiar to providers and available with a short lead time



ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications

Principal Investigators:	Adrian Hernandez, MD, MHS
	Susanna Naggie, MD, MHS
Data Coordinating Center:	Chris Lindsell, PhD
Statisticians:	Thomas G. Stewart, PhD
	Frank Harrell, PhD

ACTIV-6

Motivating questions

How to help someone *feel better faster* with newly diagnosed mild-moderate COVID-19?

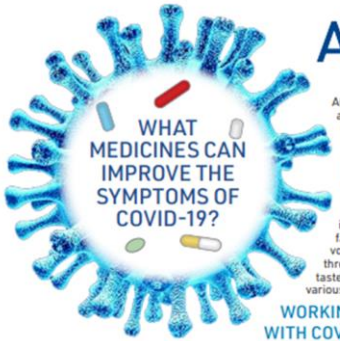
How to *prevent hospitalizations or death* in someone with newly diagnosed mild-moderate COVID-19?

The purpose of this study is to see if the medicine helps you feel better faster

AND

The purpose of this study is to see if the medicine stops the disease progressing

- *Mild-moderate Covid-19*
- *Repurposed therapies with established safety profiles that can be readily taken in an at-home setting*
- *Rapidly provide evidence to inform providers and patients that are considering these options*
- *Support approval for this use should that be appropriate*



ACTIV-6

ACTIV-6 is a nationwide study to test medicines that are already approved for other diseases to see if they can help people with mild to moderate COVID-19 feel better faster and stay out of the hospital. ACTIV-6 is part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program.

WHO CAN PARTICIPATE? Adults age 30 or older with COVID-19 symptoms, a positive test within the last 10 days, and at least two symptoms of the illness for seven days or less. Symptoms include fatigue, difficulty breathing, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, and/or new loss of sense of taste or smell. You may be excluded from the study for various reasons.

WORKING TOGETHER TO HELP PEOPLE WITH COVID-19 FEEL BETTER FASTER.

WHAT ARE THE STEPS IN THIS STUDY?

1 SIGN UP ONLINE

People can participate from anywhere in the US. After signing up online, by web or phone, you will get an email or text message within a day with a link. That link will take you to the registration survey.

2 ABOUT THE MEDICINES

This study is testing several different medicines. You will be selected by chance to get either a medicine you are eligible for or a placebo. Learn about the medicines here.

CLINICAL STUDIES AND PLACEBOS

Participants in this study take either a study medicine or a placebo. A placebo is a medication that has no active ingredients and will have no effect on you. When some people take medicines and others take placebos, that lets researchers figure out if a medicine is useful or not.

3 CHOOSE THE MEDICINES YOU WOULD WANT TO TRY

Participating in this study involves: **1)** choosing which medicines you'd be willing to take, **2)** taking the medication assigned to you, and **3)** keeping track of your symptoms by using online surveys. No one, including you, will know if you're taking a medicine or a placebo.

Your chance of taking a medicine instead of a placebo depends on how many medicines you are willing to try and are eligible for:

Choose 1, your chance is 50% (1 out of 2)

Choose 2, your chance is 67% (2 out of 3)

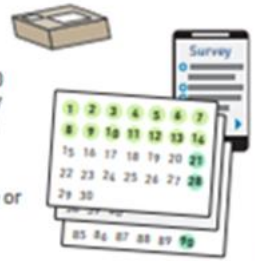
Choose 3, your chance is 75% (3 out of 4)

4 RECEIVE AND TAKE YOUR MEDICATION, COMPLETE DAILY SURVEYS

Your medication will be mailed to your home at no cost, and then you will start taking it according to its instructions.

You will be asked to answer a short (5 to 10 minutes) survey on a secure website every day for 14 days, and follow-up surveys on days 21, 28 and 90.

If you still have symptoms after 14 days, you'll take a daily survey until they're gone or you reach day 28. If you feel worse at any time, you should seek medical care as you normally would and notify the study team during the next survey.



There are no in-person visits involved with this study. You can stop participating in the study at any time.

5 GET YOUR REWARD

You will receive gift cards on the 28th and 90th day that total $100.

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AND

The purpose of this study is to see if the medicine stops the disease progressing

- *Mild-moderate Covid-19*
- *Repurposed therapies with established safety profiles that can be readily taken in an at-home setting*
- *Rapidly provide evidence to inform providers and patients that are considering these options*
- *Support approval for this use should that be appropriate*

Symptoms or signs ?

Patient Reported Outcomes –v– Researcher Observed Outcomes

Both?

SYMPTOMS

- Fatigue
- Dyspnea
- Fever
- Cough
- Nausea
- Vomiting
- Diarrhea
- Body aches
- Chills
- Headache
- Sore throat
- Nasal symptoms
- New loss of sense of taste or smell
- Other COVID-related symptom

CLINICAL EVENTS

- Hospitalization
- Death

Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2020
Clinical/Medical

← Guidance Doc

↓

Table 1. Example of an Assessment of 14 Common COVID-19-Related Symptoms: Items and Response Options

Example items *For items 1–10, sample item wording could be: "What was the severity of your **[insert symptom]** at its worst over the last 24 hours?"*	**Example response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	

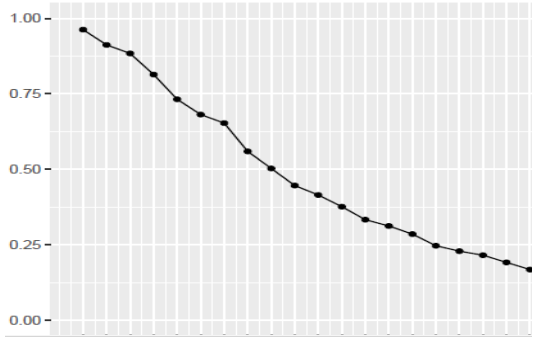
e.g. common symptoms in Covid

- Any symptoms
- Fatigue
- Dyspnea
- Fever
- Cough
- Nausea
- Vomiting
- Diarrhea
- Body aches
- Chills
- Headache
- Sore throat
- Nasal symptoms
- New loss of sense of taste or smell

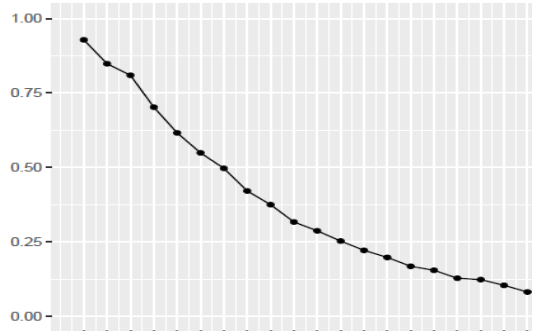
How to combine or measure:

- Number
- Severity
- Duration
- Impact on daily life
- Recovery

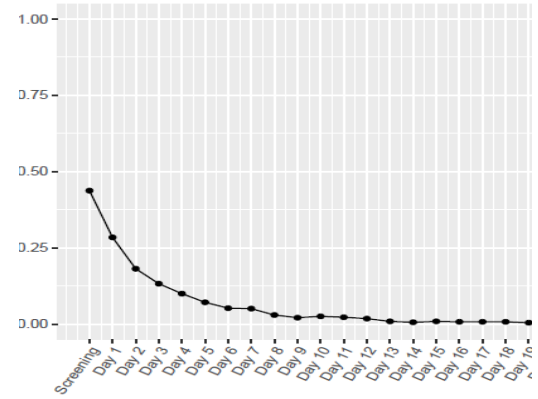
Any



Fatigue



Fever



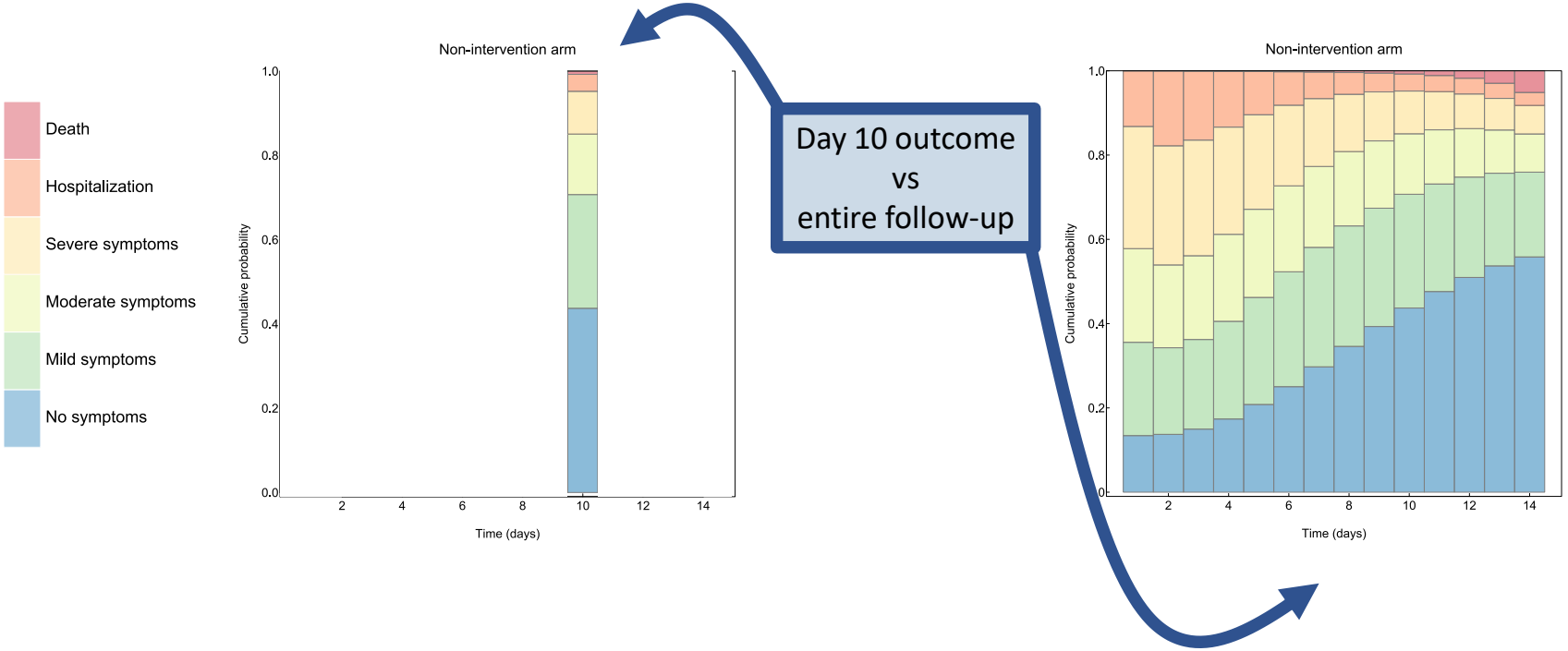
How to count symptoms and events?

Current approach

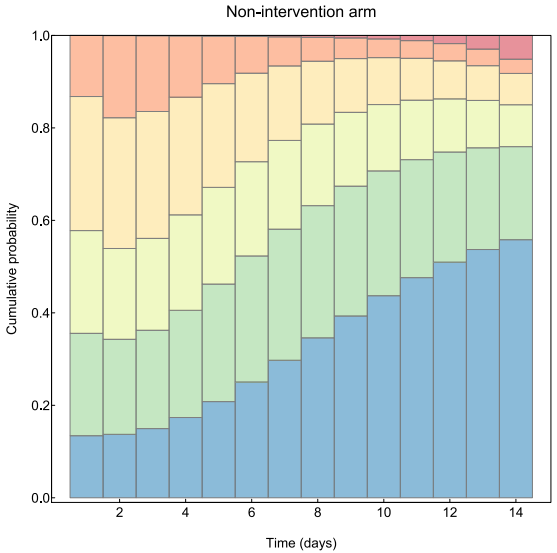
Score	Description
0	Patient reports no symptoms
1	Patient describes the overall symptom burden as mild
2	Patient describes the overall symptom burden as moderate
3	Patient describes the overall symptom burden as severe
4	Hospitalization
5	Death

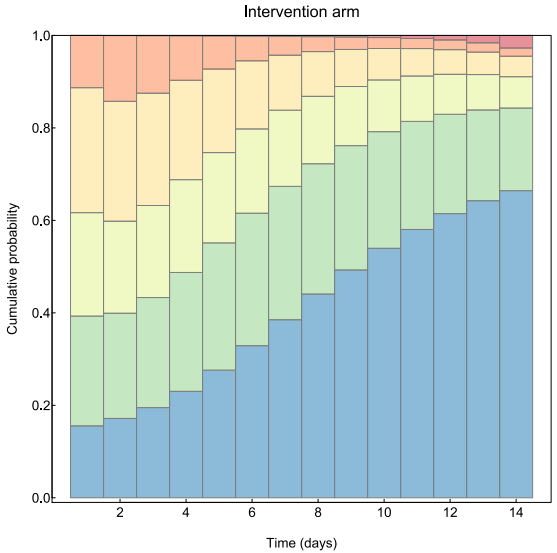
How does the measurement translate to an outcome?

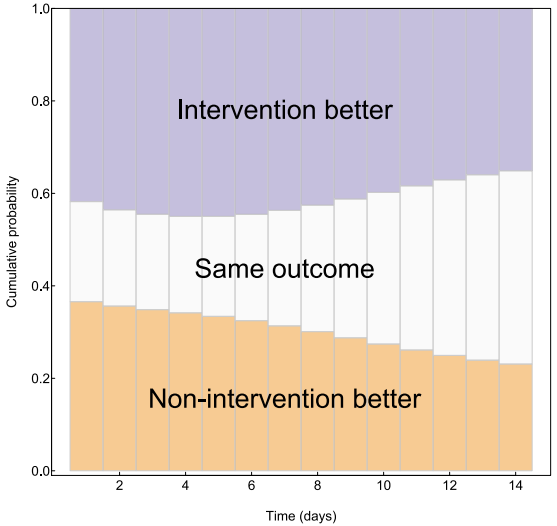
- Make maximal use of longitudinal outcome data



Days benefit

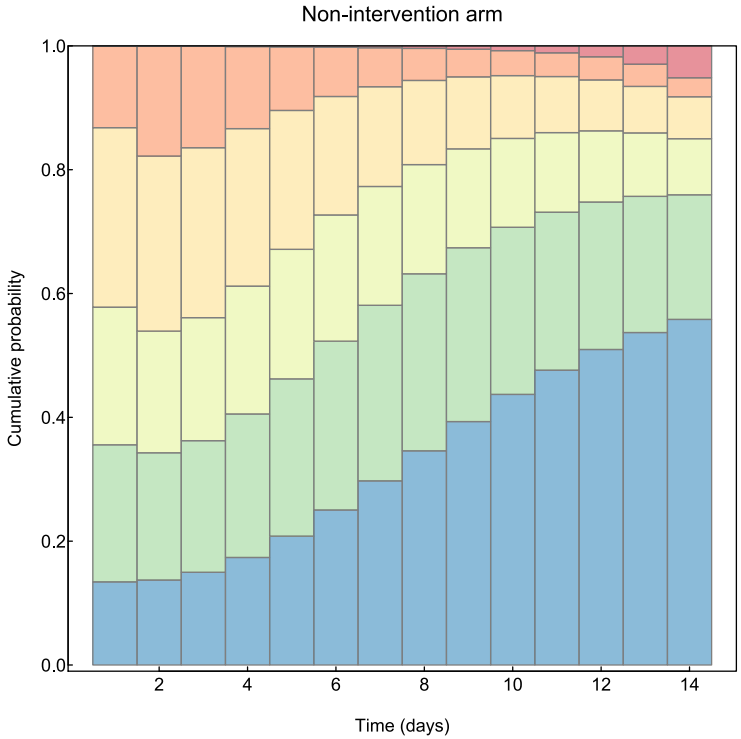


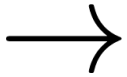


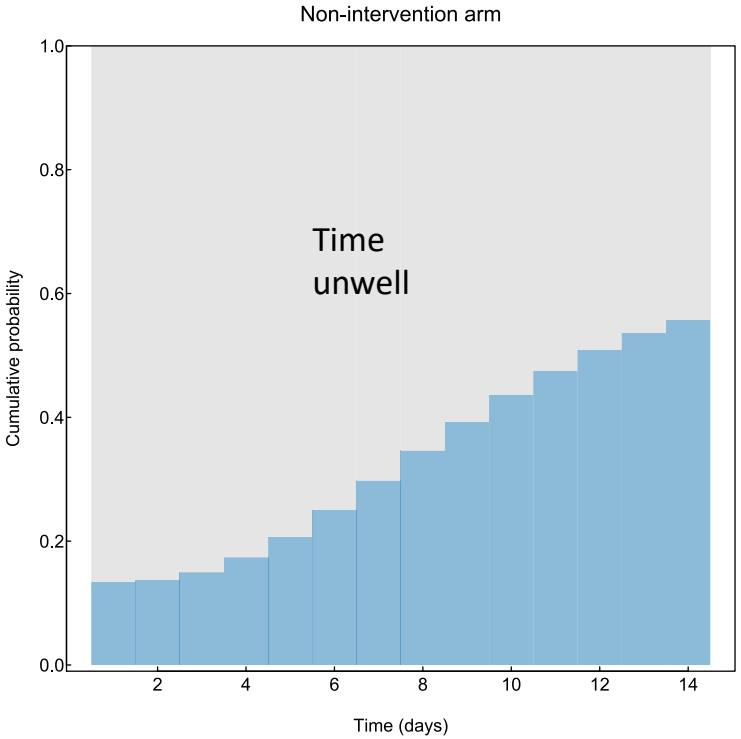


Intervention better	5.8 days
Same outcome	4.0 days
Non-intervention better	4.2 days
Days benefit	1.6 days

Mean Time Unwell





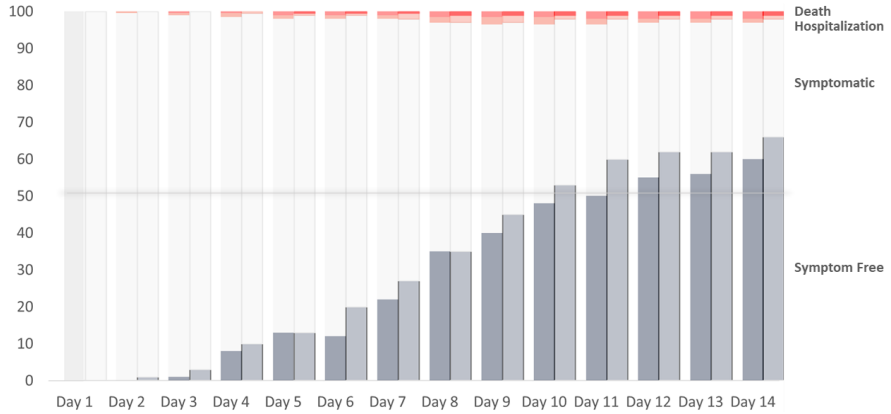


Measurements

No symptoms
Mild symptoms
Moderate symptoms
Severe symptoms
Hospitalization
Death

Symptoms
Clinical

Outcomes



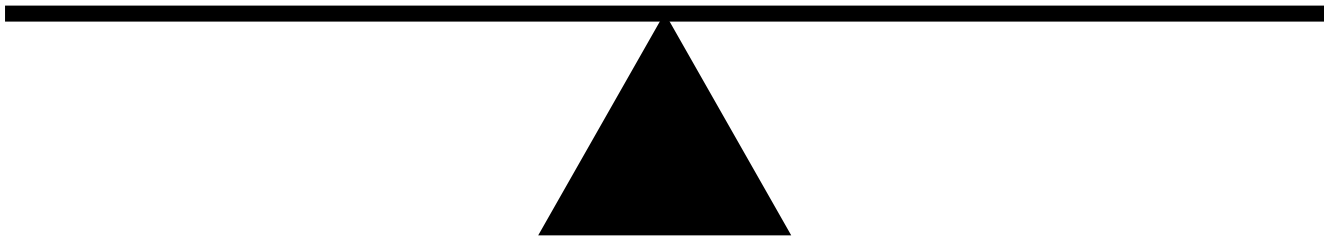
Model-based estimand
Days of benefit

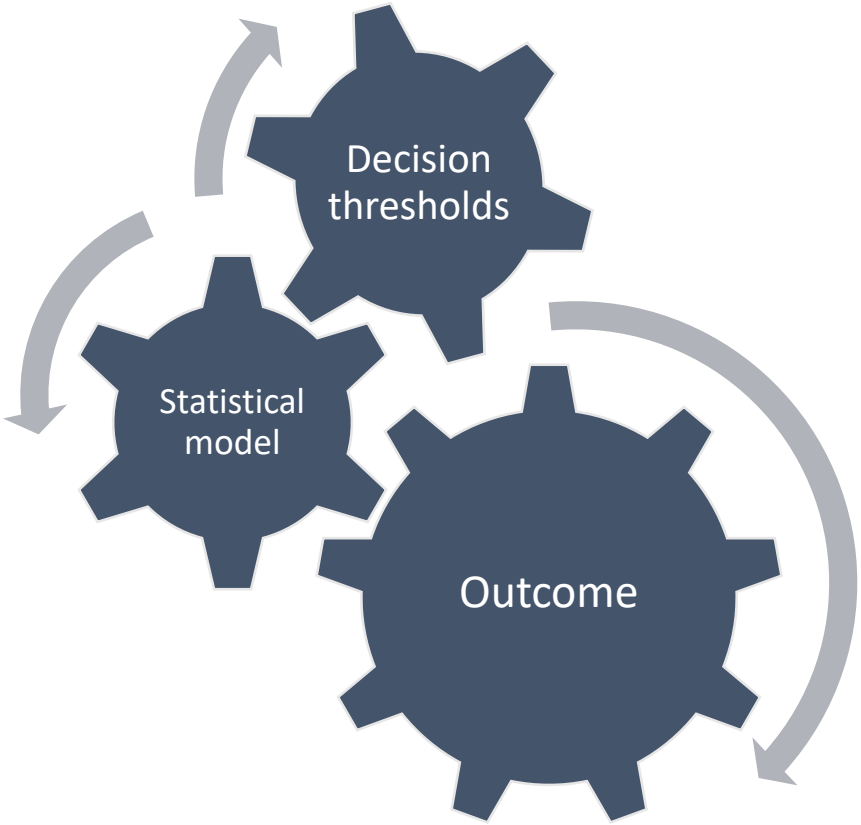
The outcome is designed to be highly sensitive and very pragmatic, and to provide information that matters to providers and patients

There is a need to balance the strengths with the protecting the public and science from a false positive trial

Days of benefit: for early looks in the data as a screening phase for the intervention

Time to recovery / hospitalization & death: for later looks at the data as a specific test of intervention effects





➔ Does the intervention work?

Finding a unicorn may be hard (or even impossible)

What matters varies among stakeholders

Do we place too much emphasis on a single piece of information?

Searching for a unicorn:

Navigating stakeholder perspectives when selecting outcomes for outpatient trials

Christopher J. Lindsell, PhD